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3a Have you appointed an agent to deal with your application?

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⬇ ***please give details below***

Agent's name: J. MILLER & CO.

Agent's address: 34 BEDFORD ROW
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Postcode: WC1R 4JH

Agent's ADP number: 0000114900 2

3b: *If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.*

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01 MAY 1995

9508823.3

Your reference GBP11629A

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Rule 16 of the Patents Rules 1990 the main rule governing the completion and filing of this form.

The Patent Office — Request for grant of a Patent

Form 1/77

Patents Act 1977

❶ Title of invention

1 Please give the title of the invention: DRUG DERIVATIVES

❷ Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required.

❷ Applicant's details

❑ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name: SCOTIA HOLDINGS PLC

Country *(and State of incorporation, if appropriate)*: ENGLAND

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7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

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Yes [ ] No [x] ➡ ***A Statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).***

❽ Checklist

❽ Please supply duplicates of claim(s), abstract, description and drawing(s).

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77	Nil		
Claim(s)	1	Description	23
Abstract	Nil	Drawing(s)	Nil

8b Which of the following documents also accompanies the application?

Please mark correct box(es)

Priority documents *(please state how many)*	
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Patents Form 7/77 – Statement of Inventorship and Right to Grant *(please state how many)*	
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❾ Request

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Please sign here ➡ Signed J. Miller & Co. Date 01 (day) May (month) 1995 (year)

J. Miller & Co.

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❶ Reference number

4 Agent's or applicant's reference number *(if applicable)* GBP11629A

❻ Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ ➡ ***go to 6***

↓

please give details below

❑ number of earlier application or patent number

❑ filing date

(day month year)

❑ and the Section of the Patents Act 1977 under which you are claiming:

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15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

❶ Declaration of priority

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Country of filing	Priority application number *(if known)*	Filing date *(day, month, year)*

actions into the body, and as a result more and more compounds are being administered by variations of patch technology.

All three barriers, the cell membrane, the blood-brain barrier and the skin have an important feature in common, they are substantially composed of lipids. What this means is that they are impermeable to primarily water-soluble drugs unless these drugs can be carried across the membrane by a receptor or transport system. In contrast, lipophilic substances are able to cross the barriers readily without the need for any specific receptor or transport system.

THE INVENTION : THE BASIC IDEA OF FATTY ACID DERIVATIVES; SOME OF THE EFFECTS OF THE FATTY ACIDS THEMSELVES

We have developed a technique or method for improving the transport of drugs across lipid membranes by linking them directly or via intermediate links to, in particular, gamma-linolenic acid (GLA) or dihomo-gamma-linolenic acid (DGLA), two fatty acids which in themselves have a range of desirable effects. Other fatty acids, such as any of the essential fatty acids (EFAs) and in particular the twelve natural acids of the n-6 and n-3 series EFAs, can be used or indeed any fatty acid which has two or more cis or trans carbon-carbon double bonds, and use may be in the form of the fatty acid or the corresponding fatty alcohol. References to fatty acids are accordingly to be read herein as to both forms, except where the chemistry of one or the other specifically is under discussion. The desirable properties of GLA and DGLA, however, make them especially valuable for the purpose. For example, in their own right GLA and DGLA have been shown to have anti-inflammatory effects, to lower blood pressure, to inhibit platelet aggregation, to lower cholesterol levels, to inhibit cancer cell growth, to reduce dyskinetic movements, to relieve breast pain, to

Title: Drug Derivatives

FIELD OF INVENTION

The invention relates to drug derivatives, the term drug being understood in the widest sense of a bioactive compound to be administered to the human or animal body.

BACKGROUND

Many drugs act at the cell membrane surface by combining with cell surface receptors, or alternatively are taken into cells by specific transport systems. However, there are many drugs which, while they act within cells by modifying one of many different functions, such as nucleic acid functions, the actions of intracellular enzymes, or the behaviour of systems like the lysosomes or the microtubules, are not able to penetrate cells effectively. There may be no receptors and transport systems with which they can link, or these systems may transport the drug into the cell at a less than optimum rate.

There are other barriers to drug movements which are recognised as important. One of particular significance is the blood-brain barrier, which has many of the characteristics of the cell membrane. There are many drugs which have difficulty in reaching adequate concentrations in the brain because of this barrier. Another is the skin: until a few years ago drugs were applied to the skin only if their purpose was to act on the skin. However, it has been recognised that the skin can be an appropriate route for getting drugs with systemic

(vi) Improvement in oral absorption (eg. penicillin series - acyloxyalkyl esters).

(vii) Prevention of presystemic metabolism (eg. propanolol succinate).

(viii) Prolongation of drug delivery (eg. haloperidol decanoate).

(ix) Inprovement in site specific drug delivery (eg. methenamine - prodrug of formaldehyde for UT infections.

(x) Reduction in toxicity (eg. sulindac).

Any of the above factors may be in mind when applying the invention.

CLASSES OF DRUGS BY ROUTE

Drugs whose pharmacokinetic behaviour may be improved, listed by route of entry, are as follows:

1. Cell entry: drugs particularly likely to benefit are those that act primarily intracellularly. These include:

   a. All anti-inflammatory drugs, whether steroid or non-steroid related;

   b. All cytotoxic drugs used in the management of cancer;

   c. All antiviral drugs;

   d. All other drugs that have to enter cells in order to achieve optimum effects, in particular drugs which act on DNA or RNA, or on enzymes located intracellularly, or in second messenger systems, or on microtubules, mitochondria, lysosomes, or any other intracellular organelle.

   e. Steroid hormones and other hormones that act intracellularly, such as oestrogens, progestins, androgenic hormones and dehydroepiandrosterone.

improve calcium absorption and enhance its deposition in bone, to reduce the adverse effects of ionising radiation, to treat various psychiatric disorders, to cause vasodilation to improve renal function, to treat the complications of diabetes, to dilate blood vessels and so on. Drugs linked to GLA and DGLA will therefore not only become more lipophilic, enhancing penetration across all membranes, the skin and the blood brain barrier, but are also likely to exhibit new and additional therapeutic effects.

THE SCOPE OF THE INVENTION BROADLY

The invention extends to fatty acids carrying linking groups as described; to fatty acid drug derivatives made using them or generally; to improvement of drug transport across lipid barriers using such derivatives; and to manufacture of medicaments for improved therapy by virtue of such improved transport.

PRODRUG DESIGN GENERALLY

Classically, factors in prodrug design are as follows:

(i) Modification of taste (eg. chloramphenicol palmitate) or odour (eg. prodrugs of ethane thiol).

(ii) Reduction of pain at injection site (eg. clindamycin-2-phosphate).

(iii) Reduction of gastrointestinal irritability (eg. aspirin prodrugs).

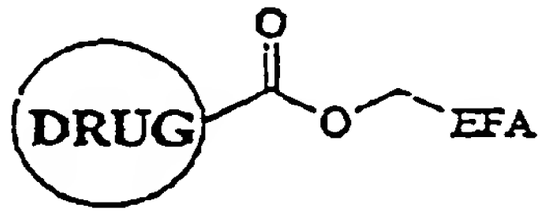
(iv) Alteration of solubility (eg. water solubility: chloramphenicol succinate; lipid solubility: 6-mercaptopurine-S, N-di-pivaloyloxymethyl derivative, lipid solubility.

(v) Increase in chemical stability (eg. azacytidine bisulphite adduct).

CLASSES OF DRUGS BY CHEMISTRY

Among the chemical classes of drugs which may be derivatised are:

(a) **drugs with a free carboxyl group** - these may be derivatised as follows:



e.g. indomethacin, ibuprofen, sulindac, penicillin V.

Some specific examples of EFA-CH_2OH are:

(i) z,z-octadeca-9,12-dienol (LA alcohol)

(ii) z,z,z-octadeca-6,9,12-trienol (GLA alcohol)

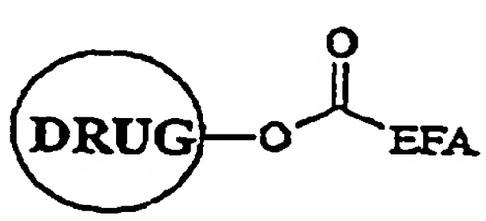
(iii) z,z,z-eicosa-8,11,14-trienol (DGLA alcohol)

iv) z,z,z,z-eicosa-5,8,11,14-tetraenol (AA alcohol)

v) z,z,z,z,z-eicosa-5,8,11,14,17-pentaenol (EPA alcohol)

vi) z,z,z,z,z,z-docosa-4,7,10,13,16,19-hexaenol (DHA alcohol)

(b) **drugs with a free hydroxyl group** - these may be derivatised as follows:



e.g. salicylic acid, metronidazole, fluphenazine, ascorbic acid.

Some specific examples of EFA-CO2H are, for both (b) amd (c), are:

(i) z,z-octadeca-9,12-dienoic acid (LA)

(ii) z,z,z-octadeca-6,9,12-trienoic acid (GLA)

2. Blood-brain barrier: all drugs acting on the central nervous system will have their transport improved by this technique. This includes all drugs used in psychiatry, all drugs used in cerebral infections with any organism or cerebral cancer and all other drugs acting on nerve cells such as anti-epileptic drugs and others.

3. Skin: as with the blood-brain barrier, all drugs that may be required to penetrate the skin to achieve a systemic effect will benefit from their conversion to a fatty acid derivative.

PROPERTIES CONFERRED

There is thus increasing evidence that very interesting properties in addition to ready passage of lipid barriers can be conferred on many drugs by making them more lipophilic. These properties include prolonged duration of action, reduction of side effects, and bypassing of first-pass liver metabolism.

Thus for example we propose the use of GLA acid or alcohol linked to a variety of drugs either directly or via a link group. One aspect of this is to increase the lipophilicity of the drug. However, rather than simply being lipophilic prodrugs, the proposed compounds must be considered as mutual prodrugs. GLA and its *in vivo* metabolites have antiviral, antibacterial, antiinflammatory and anticancer properties. By judicious choice, two active drugs (with independent modes of action) can be delivered to the targeted site; control of pharmacokinetics and, potentially, site specific delivery may be achieved.

group and where EFA represents EFA-CO_2H and EFA-CH_2OH as covered above. Some specific examples of link groups are:

(i) -O-$(CRR^1)_n$ -O- n = 1,2,3 or greater

R,R1 = H, alkyl group C1 to C4 or higher

(ii) -C(O)$(CRR^1)_n$-O- n = 1,2,3 or greater

R,R^1 = H, alkyl group as above

(iii) -C(O)$(CRR^1)_n$C(O)- n = 1,2,3 or greater

R,R^1 = H, alkyl group as above

(v) -NHCHRC(O)- R - range of groups found on normal α-amino acids

(v) -O-P(O)(O)-O-

but the invention in not limited to these.

The above given examples are representative of the following classes of drugs:

Antibiotics - ampicillin, penicillin V

Antipsychotics - fluphenazine

Antiprotozoals - dapsone, metronidazole

Antidepressants - fluoxetine, tranylcypromine

NSAIDS - sulindac

APPLICABILITY TO AMINO ACIDS AND B-GROUP VITAMINS

"The invention is particularly applicable to the amino acids and to all the B group vitamins such as riboflavin, thiamin, nicotinic acid and nicotinamide, biotin and pyridoxine. Among the amino acids, ones of particular interest are those which seem to play roles in the regulation of cell function as well as acting as components of proteins. Examples include

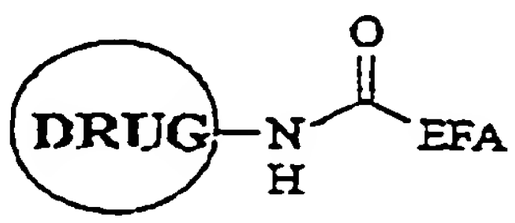
(iii) z,z,z-eicosa-8,11,14-trienoic acid (DGLA)

(iv) z,z,z,z-eicosa-5,8,11,14-tetraenoic acid (AA)

(v) z,z,z,z,z-eicosa-5,8,11,14,17-pentaenoic acid (EPA)

(vi) z,z,z,z,z,z-docosa-4,7,10,13,16,19-docosahexaenoic acid (DHA)

(c) **drugs with a free amine group** - these may be derivatised as follows:



e.g. ampicillin, dapsone, tranylcypromine, fluoxetine.

(i) z,z-octadeca-9,12-dienoic acid (LA)

(ii) z,z,z-octadeca-6,9,12-trienoic acid (GLA)

(iii) z,z,z-eicosa-8,11,14-trienoic acid (DGLA)

(iv) z,z,z,z-eicosa-5,8,11,14-tetraenoic acid (AA)

(v) z,z,z,z,z-eicosa-5,8,11,14,17-pentaenoic acid (EPA)

(vi) z,z,z,z,z,z-docosa-4,7,10,13,16,19-docosahexaenoic acid (DHA)

INTERMEDIATE LINKS

In the above derivatives are bipartate but as discussed earlier intermediate links may be used giving tripartite mutual prodrugs of the form

which are also included in the invention. The drug has a free carboxyl hydroxyl or amine

(c) by reaction of fatty acid alcohol with drug acid in the presence of a condensing agent e.g. 1,3-dimethylamino) pyridine, in an inert solvent e.g. dichloromethane, hexane at a temperature between 0° and 50°C.

(d) by reaction of fatty acid alcohol with drug acid or drug acid, short or medium chain alkyl ester or drug acid, activated ester e.g. vinyl, trifluoroethyl, in the presence of a hydrolase enzyme with or without a suitable solvent e.g. hexane, at temperatures between 20° and 80°C under conditions such that the water or alcohol byproduct formed in the reaction is removed from the reaction mixture e.g. molecular sieves or under vacuum.

(e) by reaction of drug acid with suitable fatty acid alcohol derivative e.g. tosylate, iodide with or without the presence of a suitable base e.g. potassium carbonate in a suitable inert solvent e.g. dimethylformamide and at a temperature between 0° and 180°C.

(f) by reaction of drug acid ester ($drugCO_2Y$) with fatty acid alcohol in the presence of a catalytic amount of an alkoxide of type M^+OY^- where M is an alkali or alkaline earth metal e.g. sodium, and Y is an alkyl group containing 1-4 carbon atoms which may be branched, unbranched, saturated or unsaturated. The reaction is carried out with or without a suitable solvent, e.g. toluene, at temperatures between 50 and 180°C such that the lower alcohol, HOY, is removed from the reaction mixture, e.g. by azeotropy or under vacuum.

tryptophan (a precursor of 5-hydroxy-tryptamine, 5HT, a key regulator of nerve and muscle function) and arginine, a regulator of the synthesis of nitric oxide which also plays important roles in controlling cellular activities. Among the vitamins, one of particular interest is niacin. This is able to stimulate the conversion of arachidonic acid to the powerful vasodilator prostaglandin, PGD_2. It can probably also enhance conversion of dihomogammalinolenic acid to PGE_1 and of eicosapentaenoic acid to PGI_3. The niacin derivatives of these three fatty acids and also of the arachidonic and dihomogammalinolenic acid precursor, gamma-linolenic acid, are therefore of particular interest since they combine a fatty acid with an agent which stimulates its conversion to highly desirable metabolites; PGD_2, PGE_1, and PGI_3 are all potent vasodilators and anti-thrombotic agents.

GENERAL DISCUSSION OF SYNTHESIS

A. **Mutual prodrugs in class (a) may be prepared by any reasonable method of ester synthesis and especially:**

(a) by reaction of fatty acid alcohol with drug acid chloride or drug acid anhydride with or without the presence of an organic tertiary base e.g. pyridine in a suitable inert solvent e.g. dichloromethane, toluene and at a temperature between 0° and 120°C.

(b) by reaction of fatty acid alcohol with drug acid or drug acid, short or medium chain alkyl ester, in the presence of a suitable acid catalyst e.g. p-toluene sulfonic acid, with or without a suitable inert solvent e.g. toluene, at a temperature between 50° and 180°C such that the water or alcohol formed int he reaction is removed by azeotropy or under vacuum.

(e) by reaction of fatty acid with suitable drug alcohol derivative e.g. tosylate, iodide, with or without the presence of a suitable base e.g. potassium carbonate, in a suitable inert solvent e.g. dimethylformamide and at a temperature between 1 180°C.

(f) by reaction of fatty acid ester (EFA-CO_2Y) with drug alcohol in the presence of a catalytic amount of an alkoxide of type M^+OY^- where M is an alkali or alkaline earth metal e.g. sodium, and Y is an alkyl group containing 1-4 carbon atoms which may be branched, unbranched, saturated or unsaturated. The reaction is carried out with or without a suitable solvent, e.g. toluene, at temperatures between 50° and 180°C such that the lower alcohol, HOY, is removed fro the reaction mixture, e.g. by azeotropy or under vacuum.

C. **Mutual prodrugs in class (c) may be prepared by any reasonable method of amide synthesis and especially:**

(a) by reaction of drug amine with fatty acid chloride or fatty acid anhydride with or without the presence of an organic tertiary base e.g. pyridine, in a suitable inert solvent e.g. dichloromethane, toluene and at a temperature between 0° and 120°C.

(b) by reaction of drug amine with fatty acid in the presence of a condensing agent e.g. 1,3-dicyclohexylcarbodiimide with or without a suitable organic base e.g. 4-(N,N-dimethylamino) pyridine in an inert solvent e.g. dichloromethane, hexane at a temperature between 0° and 50°C.

B. **Mutual prodrugs in class (b) may be prepared by any reasonable method of ester synthesis and especially:**

(a) by reaction of drug alcohol with fatty acid chloride or fatty acid anhydride with or without the presence of an organic tertiary base e.g. pyridine, in a suitable inert solvent e.g. dichloromethane, toluene and at a temperature between 0° and 120°C.

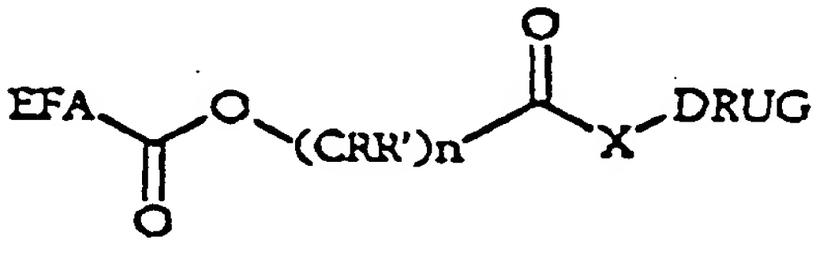
(b) by reaction of drug alcohol with fatty acid or fatty acid, short or medium chain alkyl ester, in the presence of a suitable acid catalyst e.g. p-toluene sulfonic acid, with or without a suitable inert solvent e.g. toluene, at a temperature between 50° and 180°C, such that the water or alcohol formed in the reaction is removed by azeotropy or under vacuum.

(c) by reaction of drug alcohol with fatty acid in the presence of a condensing agent e.g. 1,3-dicylohexylcarbodiimide with or without a suitable organic base e.g. 4-(N,N-dimethylamino)pyridine in an inert solvent e.g. dichloromethane, hexane at a temperature between 0° and 50°C.

(d) by reaction of drug alcohol with fatty acid or fatty acid, short or medium chain alkyl ester or fatty acid, activated ester e.g. vinyl, trifluoroethyl in the presence of a hydrolase enzyme with or without a suitable solvent e.g. hexane, at temperatures between 20° and 80°C under conditions such that the water or alcohol byproduct formed in the reaction is removed from the reaction mixture e.g. molecular sieves or under vacuum.

Hydrolysis of either of the ester groups produces an unstable 1-hydroxyalkyl ester which spontaneously releases the other acid component along with an equivalent of an aldehyde.

(c) *drug ester or drug amide of EFA acyloxy alkyl carboxylic acid*



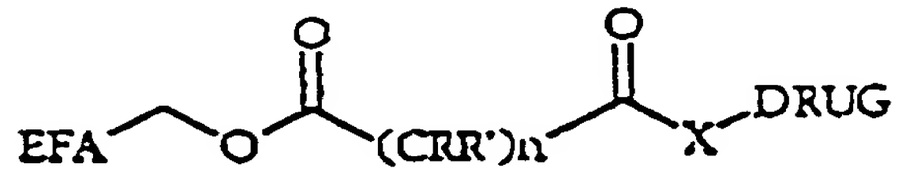
(III)

R,R^1 = H, alkyl group as above

n = 1,2,3 or greater

X = O, NH

(d) *drug ester or drug amide of EFA alkyloxyacyl alkyl carboxylic acid*



(IV)

R,R1 = H, alkyl group as above

n = 1,2,3 or greater

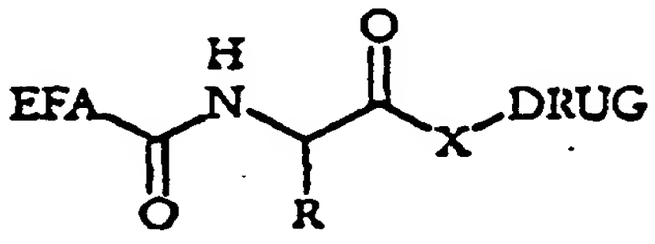
X = O, NH

(IV), n = 2, R = R^1 = H, alkyl group, C_1 to C_4 or higher, is a special case.

Hydrolysis of either of the ester groups yields a succinate or substituted succinate ester.

Intramolecular ring closure accelerates hydrolysis of the second ester group.

(e) *amino acid linkers*



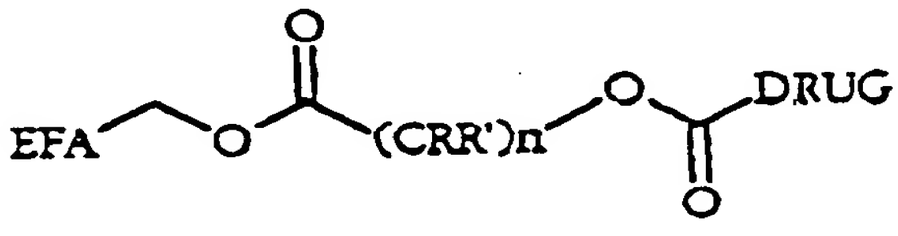
(V)

(c) by reaction of drug amine with fatty acid or fatty acid, short or medium chain alkyl ester or fatty acid, activated ester, e.g. vinyl, trifluoroethyl, in the presence of a hydrolase enzyme with or without a suitable solvent e.g. hexane at temperatures between 20° and 80°C under conditions such that the water or alcohol byproduct formed in the reaction is removed from the reaction mixture e.g. molecular sieves or under vacuum.

FURTHER DISCUSSION OF DERIVATIVES AND PROPERTIES

A further category of EFA mutual prodrugs are the tripartate prodrugs whereby the drug and EFA are connected via a link. The following classes of derivatives represent such prodrugs.

(a) *drug acyloxy alkyl carboxy esters of EFA alcohol*



(I)

R,R^1 = H, alkyl group C_1 to C_4 or higher

n = 1,2,3 or greater

(b) *drug acyloxy alkyl esters of EFA acid*

(II)

R,R^1 = H, alkyl group as above

n = 1,2,3 or greater

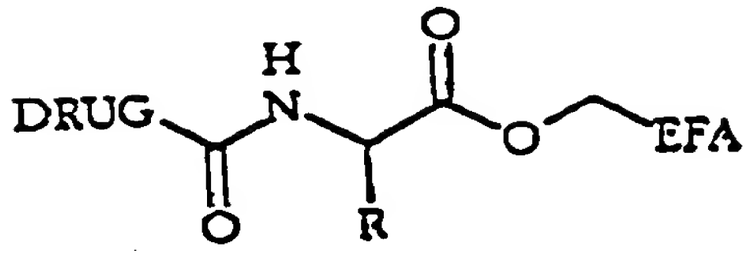
(II), n = 1, R = H, alkyl group, C_1 to C_4 or higher, R^1 = H is a special case.

As will be appreciated, the whole of the above while illustrated by reference to GLA is general, and the fatty acid or fatty alcohol compounds concerned are new in themselves and an aspect of the invention.

CONCEPTS APPLIED TO NSAIDS; EFFECTIVENESS SHOWN

As a particular example of the concepts discussed, we have prepared derivatives of various non-steroidal anti-inflammatory drugs (NSAIDs) and in particular the GLA-ester of indomethacin. Indomethacin as a non-steroidal anti-inflammatory drug is believed to have a primarily intracellular mechanism of action by inhibiting the enzyme cyclo-oxygenase, which converts arachidonic acid to pro-inflammatory prostaglandin metabolites.

Indomethacin is known to penetrate cells very poorly and so has to be given in relatively large doses which can produce many side effects, thus indomethacin-GLA was compared with indomethacin itself for its ability to penetrate cells. A high pressure liquid chromatography (HPLC) technique developed from that of Niopas, I. and Hamazoridi: K. (J. Chromatography B: 656: 447-450, 1994) allowed the separation and assay of indomethacin and its GLA ester. The ability of these two compounds to penetrate three different cell lines was tested using a normal fibroblast line, a breast cancer line and a malignant melanoma line. Each cell line was seeded into a large Petri dish and allowed to grow for 24 hours. 70 μM indomethacin or indomethacin-GLA was then added to the medium and the cells cultured for a further 24 hours. The cells at this stage were attached



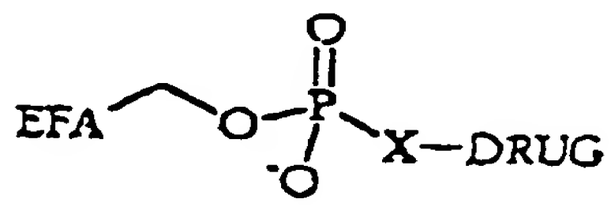
(VI)

X = NH, O

R = amino acid sidechain

Hydrolysis can then be catalysed by a range of protease enzymes. Dependent on the amino acid chosen, the link can be basic, acidic or neutral, offering a range of possibilities to modify the pharmacokinetics of the tripartate prodrug.

(f) *phosphodiester or phosphoramidate linkage*



(VII)

X = NH, O

There is evidence of increased phosphatase activity in some cancer cells (e.g. prostate). This may lead to site specific delivery of the two active components of the tripartate prodrug.

In all of the above examples EFA-CO_2H may be replaced by carboxy terminated extended analogues of EFA-CO_2H or EFA-CH_2OH. In a similar manner, EFA-CH_2OH may be replaced by hydroxy terminated extended analogues of EFA-CO_2H or EFA-CH_2OH.

Table 1

Culture	Drug	Intracellular I $\mu g/10^6$cells	Intracellular I[illegible] A $\mu/10^6$cel
ZR-1	I-GLA	168	95
ZR-2	I-GLA	78	50
ZR-3	I-GLA	217	110
ZR-4	I-GLA	555	200
ZR-5	I	Tr	-
ZR-6	I	Tr	-
ZR-7	I	Tr	-
ZR-8	I	Tr	-
SK-1	I-GLA	32	29
SK-2	I-GLA	21	23
SK-3	I-GLA	22	30
SK-4	I	0.3	-
SK-5	I	0.2	-
SK-6	I	0.4	-
Flow 1	I-GLA	428	81
Flow 2	I	Tr	-

Tr = Trace

ZR = breast cancer cell line

SK = melanoma cell line

Flow = normal cells

to the dishes. The medium was poured off and the dishes washed twice with indomethacin-free medium. Trypsin was then added to the cultures to detach the cells which were washed into a centrifuge tube and centrifuged. The supernatant was discarded and the cells were washed three times before being analysed. The cells were then extracted using the indomethacin-extraction method described by G Schollnhammer et al (J Chromatography 375: 331-8, 1986). This method is equally effective for indomethacin and indomethacin-GLA.

The results are shown in Table 1:-

Example 1.....*Indomethacin*

A solution of indomethacin (50.4 parts, g) and thionyl chloride (33.3 parts, ml) in 1,2-dichloroethane (700 parts, ml) was heated at 90°C under nitrogen for 3-6 hours. The solvent was removed *in vacuo* and further portions of 1,2-dichloroethane (2 x 200 parts, ml) were added and evaporated to remove the last traces of thionyl chloride. The dark, solid residue was dissolved in dichloromethane (700 parts, ml). To this solution was added pyridine (11.7 parts, g) and z,z,z-octadeca-6,9,12-trienol (35.4 parts, g). The mixture was stirred under nitrogen at room temperature for 24-72 hours. The mixture was then concentrated to dryness under reduced pressure and diluted with ethyl acetate. The organic layer was successively washed with brine, 2M hydrochloric acid, saturated aqueous sodium bicarbonate, and water. After drying (sodium sulfate), the solvent was evaporated to give a yellow oil which was subjected to medium pressure liquid chromatography (mplc) giving *z,z,z-octadeca-6,9,12- trienoyl-1- (4-chlorobenzoyl) -5-methoxy-2-methyl indole-3-acetate* as a yellow oil.

Examples 2-4.....*Indomethacin, Ibuprofen, Sulindac*

A solution of indomethacin (36.7 parts,g) and 4-(N,N-dimethylamino)pyridine (12.5 parts, g) in dichloromethane (100 parts, ml) was added dropwise, with stirring, over the course of 30.-120 minutes, under nitrogen, to a mixture of 1,3-dicyclohexylcarbodiimide (21.2 parts, g) and z,z,z-eicosa-8,11,14-trienol (27.3 parts,g) in dichloromethane (400 parts, ml).. Stirring was continued for 5-10 hours. The reaction was filtered, concentrated to dryness *in vacuo* and purified by mplc giving *z,z,z-eicosa-8,11,14-trienyl-1-(4-chlorobenzoyl)-5-methoxy-2-methyl indole-3-acetate* as a pale yellow oil.

In a similar manner but replacing the indomethacin with the requisite amount of 2-methyl-4'-(2-methylpropyl)-phenylacetic acid (ibuprofen) and the z,z,z-eicosa-8,11,14-trienol with z,z,z-octadeca-6,9,12-trienol there is prepared *z,z,z-octadeca-6,9,12-trienyl-2-methyl-4'-(2-methylpropyl)-phenylacetate.*

In a similar manner but replacing the indomethacin with the requisite amount of (Z)-5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-1H-indene-3-acetic acid (sulindac) and the z,z,z-eicosa-8,11,14-trienol with z,z,z-octadeca-6,9,12-trienol there is prepared *z,z,z-octadeca-6,9,12-trienyl-(Z)-5-fluoro-2- methyl-1- [[4-(methylsulfinyl)phenyl]methylene]-1H-indene-3-aceate.*

Example 5.....*Salicylic acid*

2,2,2-Trichloroethyl-z-(z,z,z-octadeca-6,9,12-trienoyl)benzoate (151 parts, g) was dissolved in a mixture of tetrahydrofuran (750 parts, ml), acetic acid (675 parts, ml) and water (75 parts, ml). Zinc dust (150 parts, g) was added. The mixture was stirred at room temperature under nitrogen for 1 - 2 hours and then allowed to stand for 10-30 hours. Excess zinc and zinc salts were filtered off through Celite, washing the filter pad with tetrahydrofuran (100 parts, ml)

As can be seen,in all cell lines the intracellular level of indomethacin after cells were incubated with indomethacin was very low and mainly detected only in trace amounts. In contrast, again in all cell lines, incubation with indomethacin-GLA resulted in very substantial amounts of both indomethacin-GLA and free indomethacin being found within the cells. These results show unequivocally that the GLA ester of indomethacin penetrates cells effectively and is then de-esterified intracellularly to provide fee indomethacin.

In view of the many similarities between the cell membrane barrier and the blood-brain and skin barriers, the indomethacin-GLA will also be effective in accelerating the penetration of indomethacin through these barriers.

Examples 8-12 .....*Metronidazole, Fluphenazine, Dapsone, Tranylcypromine, Fluoxetine*

To a suspension of metronidazole (1.9 parts, g) in dry dichloromethane (20 parts, ml) was added successively 4-(N,N-dimethylamino)pyridine (1.22 parts, g), 1,3-dicyclohexylcarbodiimide (2.2 parts, g) and linoleic acid (2.8 parts, g). The mixture was stirred at room temperature for 10-20 hours. To the reaction was added 2M hydrochloric acid (20 parts, ml) and stirring was continued. After filtration the organic layer was separated, washed with 50% saturated brine and finally saturated aqueous sodium bicarbonate. The dichloromethane solution was dried (sodium sulfate) and evaporated *in vacuo* (30°C/20mm Hg). To the resulting residue was added petrol (bp 30 - 60°C, 20 parts, ml) and the mixture allowed to stand at room temperature for 1-2 hours, causing the precipitation of the remaining urea. This was removed by filtration and the filtrate was applied to a dry column giving *2-(2-methyl-5-nitroimidazolyl) ethyl-z,z-octadeca - 9,12-dienoate* as a pale yellow, non distillable oil.

In a similar manner but replacing the linoleic acid with the requisite amount of z,z,z-eicosa-8,11,14-trienoic acid there is prepared *2-(2-methyl-5-nitroimidazoloyl) ethyl-z,z,z-eicosa-8,11,14-trienoate.*

In a similar manner but replacing the linoleic acid with the requisite amount of z,z,z,z,z,z-docosa-4,7,10,13,16,19-hexaenoic acid there is prepared *2-(2-methyl-5-nitroimidazoloyl)ethyl-z,z,z,z,z,z-docosa-4,7,10,13,16,19-hexaenoate.*

In a similar manner but replacing the metronidazole with the requisite amount of the free base of 4-[3-[2- (trifluoromethyl)10H-phenothiazin- 10-yl]]-1-piperazineethanol (fluphenazine) and the linoleic acid with the requisite amount of GLA there is prepared *4-[3-[2-(trifluoromethyl)10H-phenothiazin-10-yl]]-1-piperazineethyl-z,z,z-octadeca-6,9,12-trienoate.*

In a similar manner but replacing the metronidazole with the requisite amount of 4,4'-diamino diphenylsulfone (dapsone) and the linoleic acid with the requisite amount of GLA there is prepared *4,4'-(bis z,z,z-octadeca-6,9,12-trienoylamino)diphenylsulfone.*

In a similar manner but replacing the metronidazole with the requisite amount of *trans*-1-amino-2-phenylcyclopropane (tranylcypromine) and the linoleic acid with the requisite amount of GLA there is prepared *trans-1-(z,z,z-octadeca-6,9,12-trienoylamino)-2-phenyl cyclopropane.*

In a similar manner but replacing the metronidazole with the requisite amount of N-methyl-3-phenyl-3[α,α,α-trifluoro-p-tolyl]propylamine (fluoxetine) and the linoleic acid with the requisite amount of GLA there is prepared *N-methyl-3-phenyl -3[α,α,α-trifluoro-p-tolyl] propyl, z,z,z-octadeca-6,9,12-trienamide.*

and the filtrate was evaporated at 25°C, 0.5 mm Hg. The resulting oil was dissolved in diethyl ether (1000 parts, ml) and the resulting solution was washed with water. After drying (sodium sulfate), the ether was evaporated (25°C, 10mm Hg) to give a pale yellow oil which was subjected to a dry column giving *2-(z,z,z-octadeca-6,9,12- trienoyl)benzoic acid* as a pale orange oil which solidified to a wax in the refrigerator.

The 2,2,2-trichloroethyl-2-(z,z,z-octadeca-6,9,12-trienoyl) benzoate in the above example was prepared by the following method.

To a solution of 2,2,2-trichloroethyl salicylate (104 parts, g) in dry pyridine (500 parts, ml) at 0-5°C and under nitrogen was added z,z,z-octadeca-6,9,12-trienoyl chloride (137.5 parts, g) dropwise over a period of 1-2 hours. The reaction mixture was allowed to stir at room temperature for 10-30 hours and the pyridine was then removed *in vacuo*. The residue was dissolved in diethyl ether (2000 parts, ml) and water (1000 parts, ml) and the resulting two phase system was shaken and acidified slowly to pH1 by addition of 2M hydrochloric acid. The diethyl ether layer was separated and washed with water (4 x 1000 parts, ml), adding sodium chloride to break any emulsion that formed. After drying the organic layer (sodium sulfate), the solvent was removed *in vacuo* to give an orange/brown oil. This was purified by mpl to give 2,2,2-trichloroethyl-2-(z,z,z- octadeca-6,9,12-trienoyl) benzoate as a pale yellow oil.

Example 6....*Metronidazole*

To a suspension of metronidazole (206 parts, g) in anhydrous acetonitrile (2300 parts, ml) and anhydrous pyridine (107 parts, ml) was added with stirring at room temperature under nitrogen z,z,z-octadeca-6,9,12-trienoyl chloride (373 parts, g) over a period of 15-45 mins shortly after the addition of the acid chloride a clear solution was formed and stirring was continued for 1-3 hours. The mixture was allowed to stand for 15 hours and the solvent was removed *in vacuo* (50°C/20mm Hg). To the residue was added ethyl acetate (1000 parts, ml), any precipitated solid being filtered off. The ethyl acetate solution was washed successively with brine, 2M hydrochloric acid, saturated aqueous sodium bicarbonate solution and finally brine. After drying (sodium sulfate) the solvent was removed to give an orange oil. This material was subjected to dry column chromatography giving *2-(2-methyl-5-nitroimidazolyl) ethyl-z,z,z-octadeca - 6,9,12-trienoate* as a pale yellow, non-distillable oil.

Example7....*Metronidazole*

Metronidazole (1.9 parts, g) was suspended in toluene (30 parts, ml) and with stirring the mixture was heated under reflux with a Dean and Stark head for 10-20 mins. to remove any water present. To the boiling solution was added, under nitrogen, z,z,z-octadeca-6,9,12 - trienoyl chloride (2.96 parts, g) dropwise over a period of 10-30 mins. The mixture was stirred and heated under reflux for a further 1-3 hour to give a dark reaction mixture. After cooling, this mixture was subjected to dry column chromatography giving *2-(2-methyl -5-nitroimidazolyl) ethyl-z,z,z-octadeca - 6,9,12-trienoate* as a pale yellow, non distillable oil.

Claims: Among matters to be claimed on the basis of the above description are:-

1. A fatty acid or fatty acid alcohol, particularly with two or more cis or trans c .- carbon double bonds and more particularly an essential fatty acid of the natural n-6 or n-3 series and especially GLA or DGLA, with acyloxy alkyl carboxy ester, acyloxy alkyl ester, acyloxy alkyl carboxylic acid ester or amide, alkyloxyacyl alkyl carboxylic acid ester or amide, amino acid, phosphodiester or phosphoramidate or other group attached for chemical linking to a drug, and said fatty acid or fatty acid alcohol when so linked.

2. A drug required to cross lipid membranes in the body to exert its action, whether in entry to a cell in which the drug is to act or in passing the skin, blood-brain or other barrier, directly or indirectly linked (by a group as set out in claim 1 or otherwise) to a fatty acid with two or more cis or trans carbon-carbon double bonds, the fatty acid being as such or in the form of its fatty alcohol.

3. A drug according to claim 1 wherein the fatty acid is an essential fatty acid, particularly an essential fatty acid of the natural n-6 or n-3 series and especially GLA or DGLA.

4. A method of improving the transport of a drug across lipid membranes in the body, characterised by administration of the drug in a form as in any preceding claim.

5. A method of manufacture of a medicament for improved therapy involving transport of a drug across lipid membranes in the body, characterised by incorporating the drug in the medicament in a form as in any preceding claim.

6. Any preceding claim wherein the drug is an amino acid, a vitamin of the B group, or an antibiotic, antipsychotic, antiprotozoal, antidepressant or NSAID drug, the term drug being understood in the widest sense of a bioactive compound to be administered to the human or animal body.

Example 13....*Ampicillin*

Triethylamine (0.3 parts, ml) was added to a stirred suspension of ampicillin (0.7 parts, g) in anhydrous DMF (120 parts, ml) under a nitrogen atmosphere. To the resultant clear solution was added z,z,z-octadeca-6,9,12-trienoic acid, N-hydroxysuccinimide ester (0.75 parts, g) while maintaining the reaction at 0-10°C. The reaction was stirred at this temperature for an additional hour before allowing the mixture to stand at room temperature overnight. Tlc analysis (40% THF/hexane) at this point indicated that most of the succinimide ester had reacted. Water (40ml) was added to the reaction flask and the contents stirred. The solution was then neutralised and extracted with ethyl acetate. The extract was washed with water , dried (sodium sulfate) and concentrated to dryness leaving the crude product as a yellow glass. Trituration with hexane yielded *6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-4-thia -1-azabicyclo[3.2.0] heptane-2-carboxylic acid-z,z,z-octadeca-6,9,12-trienamide* as a yellow powder.